Med Trib 17

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Review of 5,300 Patient Records Finds

Antibiotic Use 'Remarkably Good' in Pa. Hospitals

By Nathan Horwitz
Medical Tribune Staff

PHILADELPHIA—A federally funded study in which five of the nation's top specialty groups are participating has found that antibiotic usage in Pennsylvania's general hospitals is "remarkably good."

Despite one major reservation, the study group reported that "most physicians" offered highly acceptable antimicrobial management to the hospitalized patient, and that such management compared well with that in teaching institutions.

The study, believed to be the largest of its kind ever conducted in randomly selected general hospitals in a single region, was organized by the American College of Physicians under a two-year federal grant to establish guidelines for antimicrobial usage under the new Professional Standards Review law.

20 Hospitals Included

Data were drawn from 5,300 patient records in 20 acute care general hospitals, and were "pleasantly surprising" in such key areas as the use of toxic agents, the taking of cultures, and completeness of record keeping, the team told the American College of Physicians in a preliminary report.

The findings showed that:

- Cultures were obtained in 55% of patients receiving antimicrobials and in more than 70% of those with infectious diseases;
- Ninety-nine per cent of patient charts were retrievable and "all were complete";
- Use of gentamycin and chloramphenicol was "creditably low."

Principal investigator Dr. Edward H. Kass, William Ellery Channing Professor of Medicine at Harvard Medical School, led the team in detailing the findings at the ACP sessions and at a press conference.

Prophylaxis Questioned

"What comes through in the study," Dr. Kass told the press, "is that most physicians in general hospitals use antimicrobial drugs well. In the use of agents with a high toxic potential, there is no evidence, for example, that physicians in general hospitals are doing anything in excess of those in teaching hospitals."

The study group, known as the Intersociety Committee on Antimicrobial Usage, is composed of representatives from the ACP, the American College of Surgeons, the American Academy of Family Practice, the American Academy of Pediatrics, the Center for Disease Control, with ex officio members from the American Medical Association and the federal Bureau of Quality Assurance. The project is funded under a $192,000 grant from the Department of Health, Education and Welfare.

A major "disquieting observation" reported by the group, was the finding that 20% of all antibiotic use stemmed from the prophylactic ad-

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'Confusion' Clouds Genetic Counseling Of Diabetic Patients

By Frances Goodnight
Medical Tribune Staff

NEW YORK—The need to update and carefully qualify the information given to diabetic patients and their families about the inheritance of this disease and its recurrence risks was emphasized here by Dr. Jonathan Zonana, of the University of California, Los Angeles, Harbor General Hospital.

Dr. Zonana said that genetic counseling in diabetes mellitus "has been an area of much confusion and disagreement"—primarily because knowledge is still lacking about the basic defect or defects underlying the diabetic phenotype.

But a growing body of evidence now indicates that diabetes is a heterogeneous group of disorders which share glucose intolerance in common, Dr. Zonana told a symposium on diabetes and other endocrine disorders presented by Cornell University Medical

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In Asthma and Emphysema

Asthmatic uses biofeedback device—consisting of collar microphone that senses breathing sounds—to control bronchospasm. Device for emphysema patients (inset) records finger pulse amplitude varying with intrathoracic pressure. See below.

Biofeedback Approach Aids Self-Control of Bronchospasm

By Michael Herrino
Medical Tribune Report

SAN DIEGO—Two new respiratory biofeedback approaches have helped bronchial asthmatics and pulmonary emphysema patients achieve self-control over bronchospasm and reduce their work of breathing, according to dual studies recently reported here.

In a controlled study of 20 adult asthmatics using wheeze biofeedback, "seven of the 12 experimental subjects reported reducing their daily intake of

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Landmark Decision May Set Precedent

Court's Logic in Quinlan Life-Support Case

Medical Tribune Report

This is the first of two articles detailing the reasoning of the New Jersey Supreme Court in its Quinlan decision.

TRENTON, N.J.—The unanimous decision of the New Jersey Supreme Court, authorizing Joseph Quinlan to seek medical concurrence with his opinion that extraordinary measures to maintain his adopted daughter Karen's life should be abandoned, provides a far-reaching legal basis for the termination of treatment in so-called hopeless cases. The decision was based on both federal and state constitutional rights of privacy.

'Ethics' Committees Seen

With the withdrawal of all opposition by the original treating physician, the hospital, and the lower court-appointed guardian, as well as N.J. Attorney General William F. Hyland and the county prosecutor, who originally opposed Mr. Quinlan's suit for abandonment of the life-support system on criminal grounds, the decision appears unchallenged.

The decision requires the Quinlan family to seek concurrence of treating physicians, whom they may designate, and of a hospital "ethics" committee in their belief that Karen's case is hopeless. If such concurrence is won, the committee would authorize withdrawal of the respirator that maintains her life.

The formation of "ethics committees" in hospitals where they do not now exist is expected.

The landmark decision specifically

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making rounds at press time

HHH CARCINOMA-IN-SITU - Medical team that examined Sen. Hubert H. Humphrey's bladder tumor at end of April, has announced it will drop prophylactic use of thiotepa, prescribed for their famous patient since 1972. No further treatment is planned, but HHH will be re-examined semi-annually. Team is calling the tumor a carcinoma-in-situ, although Dr. W. Dabney Jarman, George Washington urologist who heads Senator's medical group, said he prefers "dysplasia." On the other hand, Dr. F. K. Mostofi, team's pathologist, says the growth is histologically carcinoma but continues to be non-invasive. Senator's personal physician Dr. Edgar Berman, disagrees with the pathologist: "Anything that isn't invasive isn't cancer," he said.

Biofeedback Approach Aids Control of Bronchospasms

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inhaled bronchodilators between 25% and 100%," Dr. Brian Tiep, director of the Pulmonary Rehabilitation Department at City of Hope National Medical Center in Duarte, told the San Diego Biomedical Symposium. "Four of these patients reduced their daily intake of [corticosteroid] by 5 to 10 mg," he added.

More Active Lives

Two other asthmatics reported more active daily lives, although their intake of medication stayed the same. "Our work is based on devices designed specifically for the respiratory patient," Dr. Tiep later told MEDICAL TRIBUNE.

"We pick up on a respiratory signal, and this is the thing that makes our biofeedback different. We've also been lucky enough to have a signal that people can relate to—their own breath tones."

The two devices, invented by Dr. Tiep, are the wheeze biofeedback device, for asthmatics, and the intrathoracic pressure biofeedback device, for emphysema patients. The former "consists of a cardiac microphone which senses respiratory sounds transmitted to the neck," Dr. Tiep said.

The sounds, he noted, yield two outputs: amplified breath sounds and voltage oscillator. The latter rises in pitch when the patient breathes harshly or wheezes. "Patients . . . learn control by lowering the pitch of the tone."

The intrathoracic device is based on plethysmographic data indicating that finger pulse amplitude varies with alterations in intrathoracic pressures caused by breathing, Dr. Tiep said. The biofeedback cue in this case is derived from a voltage signal produced by rectification and differentiation of pulse height differences. This is reproduced both as a tone and visually on a voltmeter and on a fiber-optic tracheal-bronchial display. Again, "patients with chronic obstructive lung disease are seated in front of these displays and are instructed to lower the pitch of the tone," Dr. Tiep explained.

In the controlled study, 20 asthmatics from the City of Hope patient population were taught how to use wheeze biofeedback. The eight control subjects were given the same training and a bogus biofeedback signal. After treadmill-induced bronchospasm, the patients first scored their own symptoms subjectively, then underwent a five-minute pulmonary function evaluation, including slow and forced vital capacity, forced expiration volumes (FEV_1 and FEV_3), and maximum mid-expiratory flow rate (MMFR). After a 20-minute session of the biofeedback device, they received repeat pulmonary function studies, Dr. Tiep reported.

Subjects showed significant improvements, especially in FEV_1 and MMFR, when compared to controls. Notably, they achieved a 26.8% improvement in MMFR, compared to a 2.7% mean improvement in controls, and a 16.7% improvement in FEV_1 compared to 3.2% mean improvemeot in controls, Dr. Tiep reported.

Reduced Breathing Work

He also noted that many experimental subjects were eventually able to use self-control alone during episodes of acute bronchospasm, rather than resorting to inhaled medications. At first, they said it took 15 to 20 minutes to gain control over their breathing, but after several months of wheeze biofeedback training, many could overcome their symptoms in less than three minutes, Dr. Tiep said.

In a related pilot study of nine emphysema patients, subjects received a similar battery of pulmonary function studies before and after two weeks of intrathoracic pressure biofeedback training with an esophageal balloon. In these patients, "the work of breathing appeared to be the only sensitive indicator of change . . . since there was no change in spirometry," Dr. Tiep said. However, "most patients showed substantial reduction in their work of breathing, not simply reflecting a reduction in respiratory frequency."

Despite quantitative studies such as these, Dr. Tiep told MEDICAL TRIBUNE that "it's difficult to get a grant for a good biofeedback project, except from an agency that's interested in the psychological type of research.

"The Lung Association, for example, while they *say* biofeedback is great, don't want their name attached to it in terms of a grant. Likewise, at the NIH, there are pitifully few grants in this area, and they go only to extremely well-known people.

Occult Area?

"Because biofeedback is new, and because a lot of claims have been made for it, it's been put into the area of the occult in the minds of a lot of people," Dr. Tiep observed.

It is relatively easy, he noted, to get grants for drug research, "because drug companies need to document drug research and so on, but when it comes to something like this that offers the patient an alternative, everyone says it's the wave of the future—but they are afraid. Nevertheless, many asthmatics have already benefited from it."

While the American College of Chest Physicians did not recognize any biofeedback studies at its last conference, Dr. Tiep said, "It's a new area. It should be presented."

Logic Behind Court Decision In Quinlan Life-Support Case

Continued from page 1

attempts to lay a legal groundwork that would protect physicians from malpractice suits as well as criminal and civil proceedings in such cases. The court rejected existing medical practices and ethical concepts, which were the grounds on which the lower state court denied Mr. Quinlan's original petition for removal of his daughter's respirator. The lower court's denial was based largely on the testimony of Dr. Robert J. Morse, her neurologist, that to withdraw the respirator would violate his concept of medical standards, practices and ethics.

Contrary to some news accounts that interpreted the decision as bringing lawyers into medical decisions, the court action leaves the question of terminating treatment in a "hopeless" case in the hands of the family and physician and provides a mechanism that particularly protects the physicians. Unreported in many lay press accounts were the court's close focus on the hopelessness of the case and on the physicians' testimonies concerning their practices in terminal illness.

DR. KAREN TEEL

Moreover, in seeking a solution that would change current medical practices and standards, the court drew heavily upon the proposal of a Texas pediatrician, Dr. Karen Teel, director of pediatric education at Brockenridge Hospital in Austin, Tex., calling for establishment of an "ethics committee" in hospitals. Upon proper deliberation with the family, such committees could authorize withdrawal of life-sustaining equipment in hopeless cases. Her proposal was published in the *Baylor Law Review* (6:8-9), 1975.

In addition, in its review of the 1968 Ad Hoc Committee of Harvard Medical School's advocacy of the utilization of "brain death" as a criterion, the court noted that the Committee had pointed out that "it is unsound and undesirable to force the family to make the decision" to stop the respirator. Thus the role of the physicians is enlarged and protected.

What the court emphasized as the critical question was medical testimony that Karen could not recover despite "extraordinary" efforts in contrast to cases in which the patient was restored to health by such measures.

Relevant medical, religious, philosophical and constitutional concepts as well as the medical data and legal proceedings that brought Karen Quinlan's case before the court were examined in its 59-page decision by Chief Justice Richard J. Hughes.

Guardian's Character

Discussing the character and motivation of Mr. Quinlan "as guardian for his daughter," the court noted that "the proofs showed him to be deeply religious, imbued with a morality so sensitive that months of tortured indecision preceded his belated conclusion (despite earlier moral judgments reached by other family members but unexpressed by them in order not to influence him) to seek the termination of life-supportive measures sustaining Karen." The court also reviewed the position of the Catholic church, of which the Quinlans are devout members and which, in a statement by Bishop Casey, found Mr. Quinlan's decision "*morally correct.*" [Bishop Casey's emphasis—Ed.]

Even if Mr. Quinlan were a Buddhist, an agnostic or atheist, the court emphasized, "and his moral judgments were formed without reference to religious feelings but were nevertheless formed and visible, we would with equal attention and high respect consider these elements."

In recent years, the New Jersey Supreme Court has become one of the outstanding judicial bodies in the nation because it has dealt courageously with profoundly difficult societal problems, including the alleged "frame-up" on murder charges of "Hurricane" Carter, the boxer.

The Quinlan case rose to national prominence when Karen's parents sorrowfully sought, after months of seeing their comatose daughter deteriorate and hearing her doctors describe her condition as being irremediable, to have the respirator sustaining her life quietly withdrawn. As indicated earlier, her treating physician had refused to do this on grounds that it was not in accord with medical practice standards. His view was supported by the hospital and other physicians.

"Undreamed of" Technology

As a result, since Karen was incompetent, her father petitioned a lower court to be appointed his 22-year-old daughter's legal guardian with the express power to discontinue "all extraordinary medical procedures" since these efforts "present no hope of her eventual recovery." Because what he sought interfered with their views of their proper functions, Quinlan's petition was opposed by the treating physicians, the hospital, the county prosecutor and the state Attorney General. In the lower court Judge Muir denied Mr. Quinlan's petition, supporting the view of the physicians that they must act in accordance with medical practice standards, and divided the guardianship of Karen, giving her father guardianship of her "trivial property" and awarding guardianship of her person to a stranger. As a result, Mr. Quinlan appealed to the New Jersey Supreme Court for full guardianship with the power to discontinue his daughter's life support system.

Calling the matter "of transcendant importance, involving questions related to the definition and existence of death, the prolongation of life through artificial means developed by medical technology undreamed of in past generations," the court focused immediately on the fact that Karen's condition was considered hopeless, citing the testimony of an examining neurologist, Dr. Julius Korein:

Q. Doctor, can the art of medicine repair the cerebral damage that was sustained by Karen?

A. In my opinion, no.

Q. Doctor, in your opinion is there any course of treatment that will lead to the improvement of Karen's condition?

A. No.

Thus the court began its consideration of the issues, emphasizing "the impact of such durationally indeterminate and artificial life prolongation on the rights of the incompetent, her family and society in general; the bearing of constitutional right and the scope of judicial responsibility as to the appropriate response of an equity court of justice to the extraordinary pray for relief of the plaintiff" (Joseph Quinlan).

'Abnormal' EEG

The court examined the medical facts in some detail, noting that on the night of April 15, 1975, "for reasons still unclear, Karen Quinlan ceased breathing for at least two 15-minute periods." Given ineffectual mouth-to-mouth breathing, then admitted to Newtown Memorial hospital, she had a temperature of 100 degrees, with pupils unreactive, and was unresponsive even to deep pain. Examined three days later by a neurologist, Dr. Robert J. Morse, who became her treating physician, she was comatose "with evidence of decortication, a condition relating to derangement of the cortex of the brain causing a physical posture in which the upper extremities are flexed and the lower extremities are extended." She required a respirator and Dr. Morse concluded that prolonged lack of oxygen was associated with her condition.

Unconscious, given a tracheotomy, still on a respirator, she was transferred to St. Clare's Hospital. An electroencephalogram was "abnormal but it showed some activity and was consistent with her clinical state." She presently developed "sleep-wake" cycles; "in the awake cycle she blinks, cries out and does things of that sort but is still unaware of anyone or anything around her."

That she "is not 'brain dead' " by

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Dr. Teel Welcomes New Jersey Ruling

Informed by MEDICAL TRIBUNE that her proposal for an "ethics committee" had become part of the New Jersey Supreme Court's decision, Dr. Karen Teel said, in part: "I join the majority of physicians in this country in welcoming the judgment rendered by the New Jersey Supreme Court. It was a very thoughtful and compassionate decision, establishing, it seems to me, a landmark precedent for dealing with such circumstances. The Court acknowledged that our standards of medical practice had been very ambiguous and without actual legal foundation or sanction. Hopefully, their suggestion for the resolution in this case would remove some of the cause for that ambiguity." Her full assessment will be published in the next issue of MEDICAL TRIBUNE.

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CLINICAL NEWS NOTE: *"Skin testing is worthless unless it is correlated with a good history and physical examination. It is totally unreliable when testing for food allergy. But it has some reliability when testing for certain drugs, such as penicillin. However, the newer forms of drug testing which utilize the lymphocyte transformation technique are much more reliable.* (Dr. Earl Benedict Brown. See "In Consultation," page 13.)

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Coming Next Issue
THE GOOD DRUGS DO

Edited by the famous clinical pharmacologist, Dr. Lasagna, and designed to be removed from Medical Tribune for your waiting room, next week's installment will be devoted to rheumatoid arthritis.

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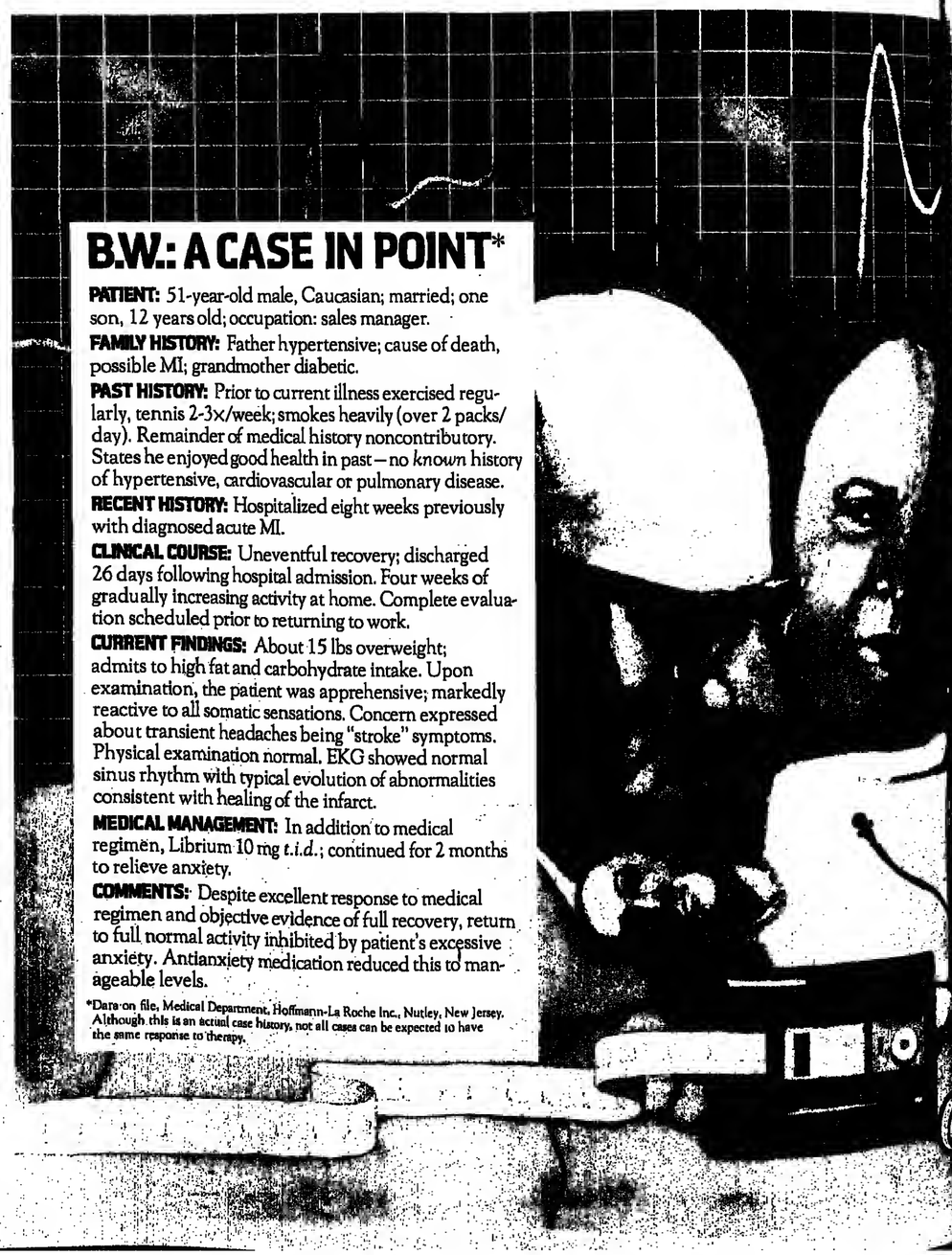

B.W.: A CASE IN POINT*

PATIENT: 51-year-old male, Caucasian; married; one son, 12 years old; occupation: sales manager.

FAMILY HISTORY: Father hypertensive; cause of death, possible MI; grandmother diabetic.

PAST HISTORY: Prior to current illness exercised regularly, tennis 2-3×/week; smokes heavily (over 2 packs/day). Remainder of medical history noncontributory. States he enjoyed good health in past—no *known* history of hypertensive, cardiovascular or pulmonary disease.

RECENT HISTORY: Hospitalized eight weeks previously with diagnosed acute MI.

CLINICAL COURSE: Uneventful recovery; discharged 26 days following hospital admission. Four weeks of gradually increasing activity at home. Complete evaluation scheduled prior to returning to work.

CURRENT FINDINGS: About 15 lbs overweight; admits to high fat and carbohydrate intake. Upon examination, the patient was apprehensive; markedly reactive to all somatic sensations. Concern expressed about transient headaches being "stroke" symptoms. Physical examination normal. EKG showed normal sinus rhythm with typical evolution of abnormalities consistent with healing of the infarct.

MEDICAL MANAGEMENT: In addition to medical regimen, Librium 10 mg *t.i.d.*; continued for 2 months to relieve anxiety.

COMMENTS: Despite excellent response to medical regimen and objective evidence of full recovery, return to full normal activity inhibited by patient's excessive anxiety. Antianxiety medication reduced this to manageable levels.

*Data on file, Medical Department, Hoffmann-La Roche Inc., Nutley, New Jersey. Although this is an actual case history, not all cases can be expected to have the same response to therapy.

THE ANXIOUS PATIENT WITH ORGANIC CARDIOVASCULAR DISEASE

CLINICAL ANXIETY IN THE CARDIAC PATIENT

ing cardiac convalescence, the patient's anxieties often be allayed through your reassurance and eling and his family's encouragement and sup-. In some patients, however, excessive anxiety can fere with medical management. When this occurs, ium (chlordiazepoxide HCl) may be a beneficial ct.

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Librium is used concomitantly with certain ctions of other classes of drugs, such as cardiac des, diuretics, antihypertensive agents, vaso- and anticoagulants. While rare reports of le effects on blood coagulation in patients receiv- anticoagulants and Librium have been noted, l studies have not established a cause and t relationship.

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Indications: Relief of anxiety and tension occurring alone or accompanying various disease states.

Contraindications: Patients with known hypersensitivity to the drug.

Warnings: Caution patients about possible combined effects with alcohol and other CNS depressants. As with all CNS-acting drugs, caution patients against hazardous occupations requiring complete mental alertness (e.g., operating machinery, driving). Though physical and psychological dependence have rarely been reported on recommended doses, use caution in administering to addiction-prone individuals or those who might increase dosage; withdrawal symptoms (including convulsions), following discontinuation of the drug and similar to those seen with barbiturates, have been reported. Use of any drug in pregnancy, lactation or in women of childbearing age requires that its potential benefits be weighed against its possible hazards.

Precautions: In the elderly and debilitated, and in children over six, limit to smallest effective dosage (initially 10 mg or less per day) to preclude ataxia or oversedation, increasing gradually as needed and tolerated. Not recommended in children under six. Though generally not recommended, if combination therapy with other psychotropics seems indicated, carefully consider individual pharmacologic effects, particularly in use of potentiating drugs such as MAO inhibitors and phenothiazines. Observe usual precautions in presence of impaired renal or hepatic function. Paradoxical reactions (e.g., excitement, stimulation and acute rage) have been reported in psychiatric patients and hyperactive aggressive children. Employ usual precautions in treatment of anxiety states with evidence of impending depression; suicidal tendencies may be present and protective measures necessary. Variable effects on blood coagulation have been reported very rarely in patients receiving the drug and oral anticoagulants; causal relationship has not been established clinically.

Adverse Reactions: Drowsiness, ataxia and confusion may occur, especially in the elderly and debilitated. These are reversible in most instances by proper dosage adjustment, but are also occasionally observed at the lower dosage ranges. In a few instances syncope has been reported. Also encountered are isolated instances of skin eruptions, edema, minor menstrual irregularities, nausea and constipation, extrapyramidal symptoms, increased and decreased libido—all infrequent and generally controlled with dosage reduction; changes in EEG patterns (low-voltage fast activity) may appear during and after treatment; blood dyscrasias (including agranulocytosis), jaundice and hepatic dysfunction have been reported occasionally, making periodic blood counts and liver function tests advisable during protracted therapy.

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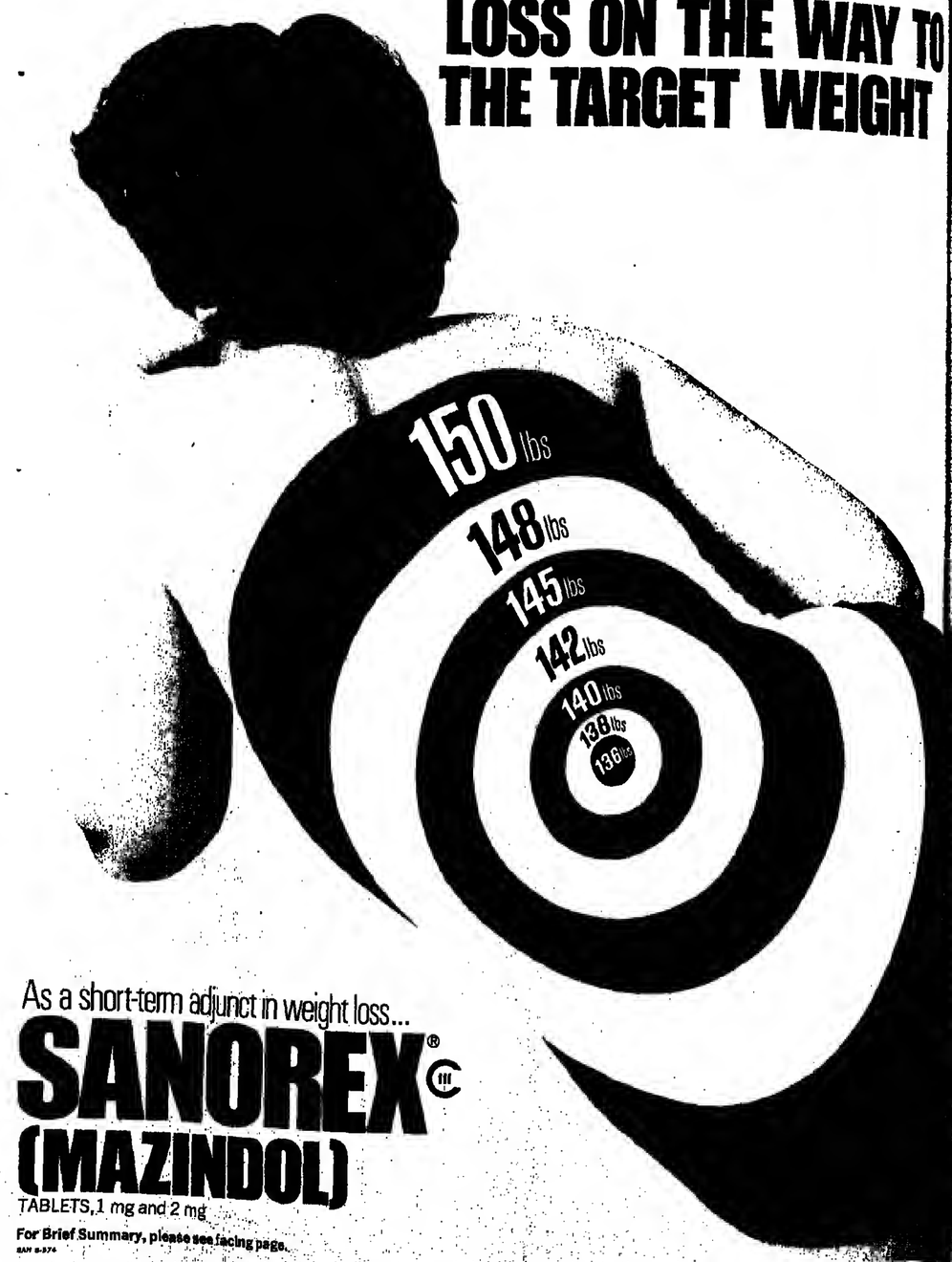

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Warnings: Tolerance to many anorectic drugs may develop within a few weeks; if this occurs, do not exceed recommended dose, but discontinue drug. May impair ability to engage in potentially hazardous activities, such as operating machinery or driving a motor vehicle, and patient should be cautioned accordingly.

Drug Interactions: May decrease the hypotensive effect of guanethidine; patients should be monitored accordingly. May markedly potentiate pressor affect of exogenous catecholamines; if a patient recently taking mazindol must be given a pressor amine agent (e.g. levarterenol or isoproterenol) for shock (e.g., from a myocardial infarction), extreme care should be taken in monitoring blood pressure at frequent intervals and initiating pressor therapy with a low initial dose and careful titration.

Drug Dependence: Mazindol shares important pharmacologic properties with amphetamines and related stimulant drugs that have been extensively abused and can produce tolerance and severe psychologic dependence. Manifestations of chronic overdosage or withdrawal with mazindol have not been determined in humans. Abstinence effects have been observed in dogs after abrupt cessation for prolonged periods. There was some self-administration of the drug in monkeys. EEG studies and "liking" scores in human subjects yielded equivocal results. While the abuse potential of mazindol has not been further defined, possibility of dependence should be kept in mind when evaluating the desirability of including the drug in a weight-reduction program.

Usage in Pregnancy: An increase in neonatal mortality and a possible increased incidence of rib anomalies in rats were observed at relatively high doses.

Although these studies have not indicated important adverse effects, the use of mazindol in pregnancy or in women who may become pregnant requires that potential benefit be weighed against possible hazard to mother and infant.

Usage in Children: Not recommended for use in children under 12 years of age.

Precautions: Insulin requirements in diabetes mellitus may be altered. Smallest amount of mazindol feasible should be prescribed or dispensed at one time to minimize possibility of overdosage. Use cautiously in hypertension, with monitoring of blood pressure; not recommended in severe hypertension or in psychotic cardiovascular disease including atherosclerosis.

Adverse Reactions: Most commonly, dry mouth, insomnia, constipation, nervousness, and insomnia. *Cardiovascular:* Palpitation, tachycardia. *Central Nervous System:* Overstimulation, restlessness, dizziness, insomnia, dysphonia, tremor, headache, depression, drowsiness, weakness. *Gastrointestinal:* Dryness of mouth, unpleasant taste, diarrhea, constipation, nausea, other gastrointestinal disturbances. *Skin:* Rash, excessive sweating, flushing. *Endocrine:* Impotence, changes in libido have rarely been observed. *Eye:* Long-term treatment with high doses in dogs resulted in some corneal opacities, reversible on cessation of medication; no such effect has been observed in humans.

Dosage and Administration: 1 mg. three times daily, one hour before meals, or 2 mg. once daily, one hour before lunch. The lowest effective dose should be used. Should GI discomfort occur, mazindol may be taken with meals.

Overdosage: There are no data as yet on acute overdosage with mazindol in humans. Manifestations of acute overdosage with amphetamines and related sympathomimetic substances include restlessness, tremor, rapid respiration, dizziness. Fatigue and depression may follow the stimulatory phase of overdosage. Cardiovascular effects include tachycardia, hypertension or circulatory collapse. Gastrointestinal symptoms include nausea, vomiting and abdominal cramps. Similar manifestations of overdosage may be expected with mazindol, their exact nature have yet to be determined. The management of acute intoxication is largely symptomatic. Data are not available on the treatment of acute intoxication with mazindol by hemodialysis or peritoneal dialysis, but the substance is relatively insoluble except at very acid pH.

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Antibiotic Use 'Remarkably Good' in Penna. General Hospitals

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ministration of antimicrobials in surgery for periods of more than 48 hours. In fact, 78% of all prophylactic courses in surgery lasted more than four days and often up to 10 and 15 days.

Dr. Kass and his colleagues stressed that they were not prepared to make a judgment about the appropriate usage of surgical prophylaxis. They noted that this is currently a controversial issue among surgeons, and that there exist no major, well-designed, large-scale studies from which firm conclusions can be drawn. The reason for characterizing the observation as "disquieting," the research group said, is the absence of studies showing that prophylaxis beyond 24 hours after surgery is useful.

That view reflected the research group's overall approach to the problem of developing guidelines in antimicrobial usage. Repeatedly, Dr. Kass and his colleagues stressed that there is still little authoritative agreement on what constitutes good practice in any but "a small portion of antimicrobial usage." Despite the clamor for regulatory action in this area, Dr. Kass declared, such regulation, if adopted, would "represent arbitrary judgments passed through debatable areas on the basis of opinions of small groups of experts," and would only lead to "serious controversy and arbitrary action."

Guidelines Being Developed

He cited surgical prophylaxis, the management of chronic bronchitis and approaches to the immunosuppressed host as examples of areas where efforts to provide guidelines would produce criteria "so broad and tentative as to be almost useless as a basis for review of professional standards and performance."

In fact, he disclosed, an initial effort by a task force of the committee's experts to set up such guidelines failed in just that way.

The committe, therefore, has made the policy decision to find out how antimicrobial drugs are actually employed by the profession and thus provide a pragmatic basis for developing guidelines grounded in common experience. Dr. Kass expressed the view that such guidelines would be acceptable to both the profession and to government reviewers.

What has emerged thus far, he said, is a preliminary picture of antimicrobial usage as it is practiced in Pennsylvania's general hospitals. The 20 institutions were chosen from among the state's 194 accredited short-term hospitals. By random techniques, 10 days evenly spaced through fiscal 1974 were selected and all patients whose hospitalization terminated on these 10 days were included in the study. From each chart, physicians and non-physician professionals abstracted a variety of data: demographic and clinical information, diagnoses, operations performed, cultural data and data related to antimicrobial administration.

The findings show that 28% of all study patients received antibiotics. Sixty-one per cent of these were, not surprisingly, on the surgical services, 30% on the medical service and 9% on the pediatric service. The percentage of patients receiving antimicrobials did not differ significantly in small, medium and large hospitals.

Ampicillin led the list of top 10 most frequently used antibiotics, with two cephalosporins occupying second and third places, and tetracycline the fourth place, followed by two penicillins.

Commenting on some of the satisfying observations, Dr. Kass told the press conference that the committee had made predictions beforehand about the frequency with which cultures would be taken "and we underestimated by a very large order of magnitude." As against the actual figure of 55% in all cases and more than 70% in infectious cases, the committee had predicted a frequency ranging from 10% to 25%, he said.

The investigator acknowledged that he did not know to what extent the Pennsylvania findings are representative of antimicrobial practices in hospitals throughout the country. "I think it would be useful to get a representative state from each of the major regions and find out," he commented.

The preliminary data thus far assembled will be completely assessed by June, and the information made available to the Intersociety Committee to use as a basis for recommending guidelines.

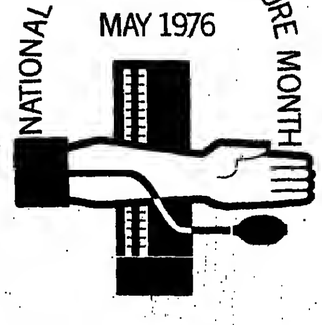
"Two features are already becoming clear," Dr. Kass stated. "It will become relatively easy to indicate certain areas in which highly commendable practices are in operation to the benefit of our patients, and certain areas in which excessive and potentially harmful practices are also in operation ... We will be able to identify practices that have no basis in data, and we will also be able to identify areas in which practices are so common, such as surgical prophylaxis, that it becomes hard to say that huge segments of the profession are entirely wrong, and equally hard to say they are right. And what that would tell us is that a need exists to organize a well-designed study to help provide an answer."

Members of the study group include Drs. George G. Jackson of Chicago, principal co-investigator; Timothy R. Townsend, CDC Medical Officer on assignment to Dr. Kass at Harvard; and Mervyn Shapiro, Instructor in Medicine, Harvard.

Nasal Contraceptive

Medical Tribune World Service

NEW DELHI, INDIA—Researchers at the All India Institute of Medical Science here are working on a contraceptive nasal spray which, to avoid side effects, contains natural rather than synthetic sex hormones. Preliminary tests conducted in rhesus monkeys suggest that the sprayed hormones rapidly reach brain sites responsible for ovulation.



Ismelin® sulfate
(guanethidine sulfate)

Esimil®
guanethidine monosulfate 10 mg
hydrochlorothiazide 25 mg

> **WARNING (Esimil)**
> This fixed combination drug is not indicated for initial therapy of hypertension. Hypertension requires therapy titrated to the individual patient. If the fixed combination represents the dosage so determined, its use may be more convenient in patient management. The treatment of hypertension is not static, but must be reevaluated as conditions in each patient warrant.

INDICATIONS
Ismelin
Moderate and severe hypertension either alone or as an adjunct.
Esimil
Hypertension. (See box warning above.)

CONTRAINDICATIONS
Guanethidine: Known or suspected pheochromocytoma; hypersensitivity; frank congestive heart failure not due to hypertension; use of MAO inhibitors.
Hydrochlorothiazide: Anuria; hypersensitivity to this or other sulfonamide-derived drugs. The routine use of diuretics in an otherwise healthy pregnant woman with or without mild edema is contraindicated and possibly hazardous.

WARNINGS
Antihypertensives are potent drugs and can lead to disturbing and serious clinical problems. Physicians should be familiar with all drugs and their combinations before prescribing, and patients should be warned not to deviate from instructions.
Guanethidine

> Warn patients about the potential hazard of orthostatic hypotension, which can occur frequently and is most marked in the morning and is accentuated by hot weather, alcohol, or exercise. To help prevent fainting, warn patients to sit or lie down with onset of dizziness or weakness, which may be particularly bothersome during the initial period of dosage adjustment and with postural changes. The potential occurrence of these symptoms may require alteration of previous daily activity. Caution patients to avoid sudden or prolonged standing or exercise while taking the drug.

Concurrent use with rauwolfia derivatives may cause excessive postural hypotension, bradycardia, and mental depression.
If possible, withdraw therapy 2 weeks prior to surgery to reduce the possibility of vascular collapse and cardiac arrest during anesthesia. If emergency surgery is indicated, administer preanesthetic and anesthetic agents cautiously in reduced dosage and have oxygen, atropine, vasopressors, and IV solutions ready for immediate use to treat vascular collapse. Vasopressors should be used with extreme caution in patients on guanethidine because of the possibility of augmented response and the greater propensity for cardiac arrhythmias.
Dosage requirements may be reduced in presence of fever. Exercise special care when treating patients with a history of bronchial asthma, since their condition may be aggravated.
Hydrochlorothiazide
Use with caution in severe renal disease. In patients with renal disease, thiazides may precipitate azotemia. Cumulative effects of the drug may develop in patients with impaired renal function.
Thiazides should be used with caution in patients with impaired hepatic function or progressive liver disease, since minor alterations of fluid and electrolyte imbalance may precipitate hepatic coma.
Thiazides may be additive or potentiative of the action of other antihypertensive drugs. Potentiation occurs with ganglionic or peripheral adrenergic blocking drugs.
Sensitivity reactions are more likely to occur in patients with a history of allergy or bronchial asthma.
The possibility of exacerbation or activation of systemic lupus erythematosus has been reported.
Usage in Pregnancy
Guanethidine: The safety of guanethidine for use in pregnancy has not been established; therefore, this drug should be used in pregnant patients only when, in the judgment of the physician, its use is deemed essential to the welfare of the patient.
Hydrochlorothiazide: Usage of thiazides in women of childbearing age requires that the potential benefits of the drug be weighed against its possible hazards to the fetus. These hazards include fetal or neonatal jaundice, thrombocytopenia, and possibly other adverse reactions which have occurred in the adult.
Nursing Mothers
Thiazides cross the placental barrier and appear in cord blood and breast milk.

PRECAUTIONS
Guanethidine: The effects of guanethidine are cumulative over long periods; initial dose should be small and increased gradually in small increments. Use very cautiously in hypertensives with: renal disease and nitrogen retention or rising BUN levels; coronary disease with insufficiency or recent myocardial infarction; cerebral vascular disease, especially with encephalopathy. Do not give guanethidine to patients with severe cardiac failure except with extreme caution.
In incipient cardiac decompensation weight gain or edema may be averted by the administration of a thiazide. Remember that both digitalis and guanethidine slow the heart rate.
Peptic ulcers or other chronic disorders may be aggravated by a relative increase in parasympathetic tone.
Amphetamine-like compounds, stimulants (eg, ephedrine, methylphenidate), tricyclic antidepressants (eg, amitriptyline, imipramine, desipramine) and other psychopharmacologic agents (eg, phenothiazines and related compounds), and oral contraceptives may reduce the hypotensive effect of guanethidine. Discontinue MAO inhibitors for at least one week before starting guanethidine.
Hydrochlorothiazide: Periodic determination of serum electrolytes to detect possible electrolyte imbalance should be performed at appropriate intervals. Observe patients for clinical signs of fluid or electrolyte imbalance (hyponatremia, hypochloremic alkalosis, and hypokalemia). Serum and urine electrolyte determinations are particularly important when the patient is vomiting excessively or receiving parenteral fluids. Medication such as digitalis may also influence serum electrolytes. Warning signs are dryness of mouth, thirst, weakness, lethargy, drowsiness, restlessness, muscle pains or cramps, muscular fatigue, hypotension, oliguria, tachycardia, and gastrointestinal disturbance such as nausea or vomiting.
Hypokalemia may develop with thiazides as with any other potent diuretic, especially during brisk diuresis, when severe cirrhosis is present, or during concomitant administration of steroids or ACTH.
Interference with adequate oral intake of electrolytes will also contribute to hypokalemia. Digitalis therapy may exaggerate metabolic effects of hypokalemia especially with reference to myocardial activity.
Any chloride deficit is generally mild and usually does not require specific treatment except under extraordinary circumstances (as in liver disease or renal disease). Dilutional hyponatremia may occur in edematous patients in hot weather; appropriate therapy is water restriction rather than administration of salt, except in rare instances when the hyponatremia is life-threatening. In actual salt depletion, appropriate replacement is the therapy of choice.
Transient elevations in plasma calcium may occur in patients receiving thiazides, particularly in those with hyperparathyroidism. Pathological changes in the parathyroid gland have been reported in a few patients on prolonged thiazide therapy.
Hyperuricemia may occur or frank gout may be precipitated in certain patients. Insulin requirements in diabetic patients may be increased, decreased, or unchanged. Latent diabetes may become manifest during thiazide administration.
Thiazide drugs may increase the responsiveness to tubocurarine. The antihypertensive effects of the drug may be enhanced in the post-sympathectomy patient. Thiazides may decrease arterial responsiveness to norepinephrine. This is not sufficient to preclude effectiveness of the pressor agent for therapeutic use.
If nitrogen retention indicates onset of progressive renal impairment, consider withholding or discontinuing diuretic therapy.
Thiazides may decrease serum PBI levels without signs of thyroid disturbance.

ADVERSE REACTIONS
Guanethidine: Frequent reactions due to sympathetic blockade—dizziness, weakness, lassitude, syncope. *Frequent reactions due to unopposed parasympathetic activity*—bradycardia, increase in bowel movements, diarrhea (may be severe and necessitate discontinuance of the drug).
Other common reactions—inhibition of ejaculation, fluid retention, edema, congestive heart failure. *Other less common reactions*—dyspnea, fatigue, nausea, vomiting, nocturia, urinary incontinence, dermatitis, scalp hair loss, dry mouth, rise in BUN, ptosis of the lids, blurring of vision, parotid tenderness, myalgia, muscle tremor, mental depression, chest pains (angina), chest paresthesias, nasal congestion, weight gain, and asthma in susceptible individuals. Although a causal relationship has not been established, a few instances of anemia, thrombocytopenia and leukopenia have been reported.
Hydrochlorothiazide: Gastrointestinal—anorexia, gastric irritation, nausea, vomiting, cramping, diarrhea, constipation, jaundice (intrahepatic cholestatic), pancreatitis. *Central Nervous System*—dizziness, vertigo.

(Brief prescribing information continued on next page)

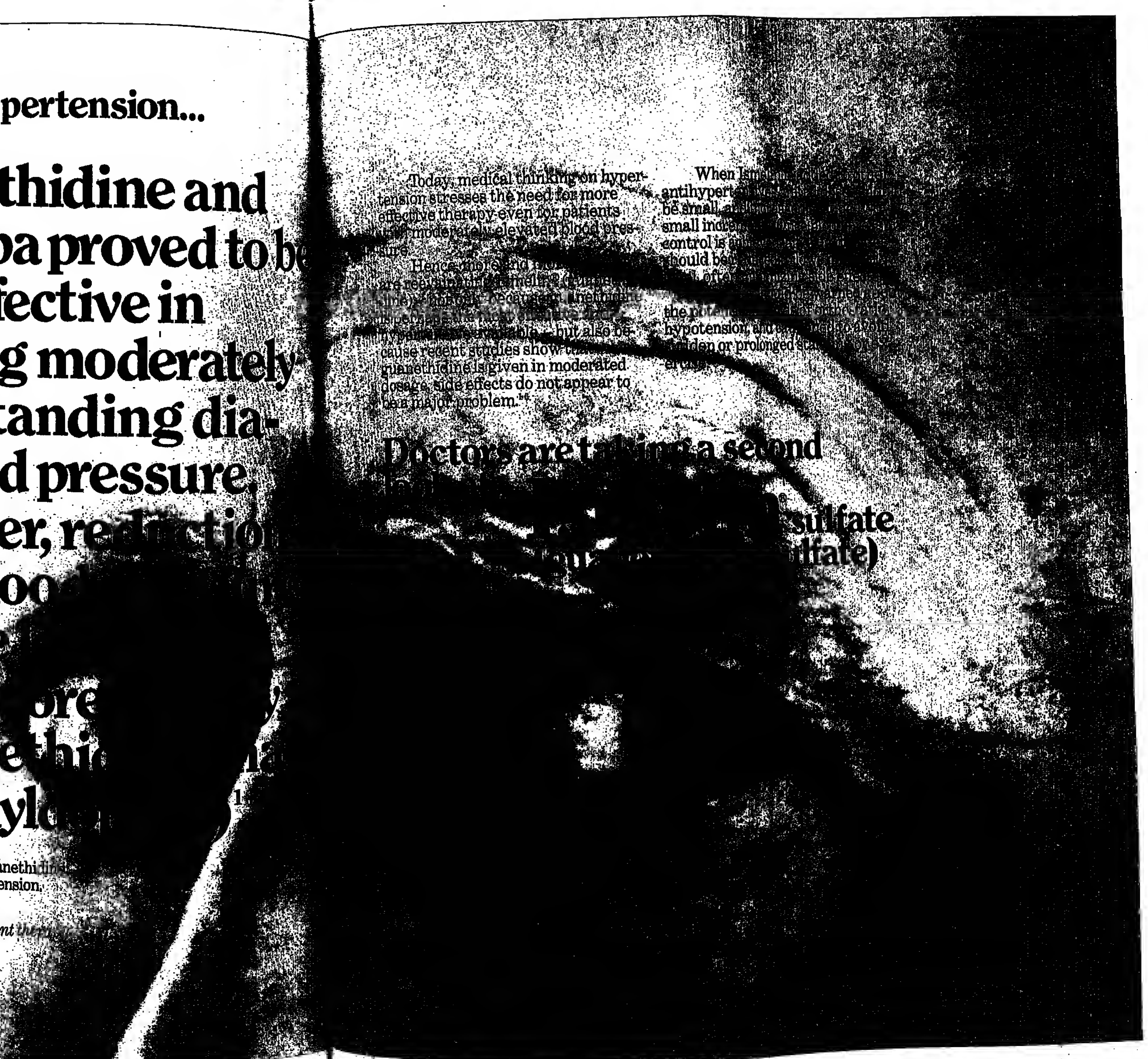
In moderate hypertension...

"Guanethidine and methyldopa proved to be equally effective in controlling moderately elevated standing diastolic blood pressure.

However, reduction of mean blood ... acceptable ... achieved more ... with guanethi... with methyl...[1]

1. Tarpley EL: Controlled trial of guanethi... and methyldopa in moderate hypertension. *Curr Ther Res* 16:1187-1196, 1974.

All patients also received concomitant th... with hydrochlorothiazide.



Today, medical thinking on hypertension stresses the need for more effective therapy even for patients ... moderately elevated blood pressure.

Hence, more and ... are ... Ismelin® ... but also because recent studies show that guanethidine is given in moderated dosage, side effects do not appear to be a major problem.[1-6]

When Ism... antihyperten... be small, and ... small incre... control is ... should be ... the poten... hypotension, and ... sudden or prolonged sta... ercise.

Doctors are taking a second ... sulfate ...lfate)

C·I·B·A

The Only Independent Weekly Medical Newspaper in the U.S.
Medical Tribune
and Medical News
Published by Medical Tribune, Inc.

Another Aspect of Thalidomide

IT IS NOW more than 14 years since the first account of the terotogenic potentialities of thalidomide appeared in MEDICAL TRIBUNE (December 25, 1961). Although the drug had superb sedative and hypnotic effects, these fell by the wayside. In this country, where the drug had still not even received approval by the FDA, the brouhaha was such that fundamental and revolutionary measures were introduced in governmental regulation of drug research and the pharmaceutical industry; there is good reason to consider some of these measures as being draconian in character.

In any event, thalidomide as an approved therapeutic agent—even when the possibility of pregnancy could not be under consideration—was officially withdrawn from use throughout the world. As an investigative agent, it is difficult to see how informed consent could be secured from any subject in this country, such has been the fear about thalidomide that has been induced by the media of communication.

But elsewhere, fortunately, studies of this highly interesting agent continued. An editorial in MEDICAL TRIBUNE (Oct. 25, 1965) mentioned that "a recent report from Israel has indicated some response to the drug in the treatment of the skin lesions of leprosy." In the interim, that work has come to fruition and, as noted in the April 7 MEDICAL TRIBUNE, Dr. Jacob Sheskin, the Israeli investigator, has received a gold medal and the title of "Benefactor of Humanity" from the World Academy of Art and Science, for the demonstration of the successful treatment of lepromatous leprosy with the use of thalidomide. As Dr. Sheskin has said, "In recent years leprosy hospitals all over the world have begun to close down because thalidomide has been accepted. Because thalidomide controls the symptoms of 'leprn reaction' doctors can now undertake long-term treatment with the sulfones without the danger of provoking previous leprn reaction."

One of the hazards of precipitate action is that of throwing out the baby with the dirty bath water. Fortunately, Dr. Sheskin did not permit that to happen. Others did.

Old Methods Still Work

LAST YEAR, THE REPORTED cases of gonorrhea in the U.S. totaled over one million; ten years ago, they were one-third that number. The threefold change is not due to any improvement in reporting of cases and now, as before, for every reported case at least two have gone unreported. This precipitous rise in the incidence of the disease appeared to have leveled off in 1975 and for unknown reasons.

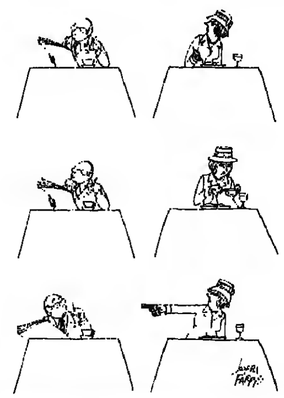
One of the research reporters on the staff of *Science* has presented a superb overview in the April 16 issue of the investigational efforts in the field of gonorrhea over the past few years. Pathogenic strains of gonococci—in contrast to those that are not—have been shown to possess pili on their surfaces, which permit them to adhere to host cells without being washed away as would occur in the urethra. With infection, the host tends to produce antibodies to the pili but the pili appear to be antigenically diverse, at least six different types having been distinguished. So, even if the antibodies have a protective effect, this would not be directed against gonococci with antigenically different pili. Nonetheless, efforts to vaccinate chimpanzees experimentally with pili have been going on with success against gonococci of the same strain of pili. It is of interest, too, that availability of iron appears to be required for pathogenicity and, in experimental systems, the presence of iron binding protein vitiates the pathogenicity of virulent gonococci.

A radioimmunoassay for pili antibodies is under study as a blood test for screening for gonorrhea, which would be of especial use in asymptomatic carriers. Other investigators are studying the membrane proteins of gonococci and some 16 different antigenic gonococci types have been classified. Perhaps this diversity of membrane and pili antigens accounts for recurrent infections and absence of immunity.

Meanwhile in Sweden the incidence of gonorrhea has done more than level off; it has fallen and is now only half of what it was in 1969. Why? Apparently because an energetic campaign has led to increased use of condoms.

Regulating Antibiotic Usage

CLINICAL QUOTE: *"To the extent that [regulatory actions] represent arbitrary judgments passed through debatable areas on the basis of opinions of small groups of experts, there is likely to be serious controversy and arbitrary action."* (Dr. Edward H. Kass, Professor of Medicine, Harvard Medical School, at the American College of Physicians meeting in Philadelphia. See p. 1).



LETTERS TO TRIBUNE

Biting, Not Stinging Bugs

Again this year I am compiling a Biting Insect Summary and would appreciate any case reports of unusual allergic reactions, especially systemic (sneezing, wheezing, urticaria) to bites of insects; i.e., mosquitoes, fleas, gnats, kissing bugs, bedbugs, chiggers, black flies, horseflies, sandflies, deerflies, etc.

I would like physicians to supply me case reports of those patients who have had unusual reactions to such insects. Include in your reports the type of reactions (immediate and delayed symptoms), treatment, the age, sex, and race of the patient, the site of the bite(s), the season of the year, and any other associated allergies.

If skin tests and hyposensitization were instituted, I would like the report of both. Please note that it is the biting (not stinging) insect in which I am interested.

If you have found any insect repellent, local treatment, or insecticides of value, I would also appreciate this.

Please send this information to me.

CLAUDE A. FRAZIER, M.D.
4-C Doctors Park
Asheville, N.C. 28801

Package Insert Omissions

In his interview with Dr. Sackier (MT, Feb. 4), Commissioner Alexander M. Schmidt of the FDA speaks nonsense when he says, "package insert is for listing indications for which there is substantial evidence of safety and efficacy." The only indications, which are listed in the package insert, are those applied for by the drug companies.

If the drug company does not apply for additional indications, they would not appear on the drug insert, even if the literature is replete with well-controlled studies demonstrating the safety and efficacy of the drug for that indication. There are any number of reasons why a drug company would not apply; including less legal liability, insufficient economic incentive for uncommon indications, harassment by FDA bureaucrats, and because the drug is largely used already for that purpose. Until the FDA and the medical and scientific community can independently institute additions to the indication section of the drug package insert, it will remain merely what the drug companies want it to be, and no more.

Commissioner Schmidt's deputy, Dr. Crout, has himself admitted that the manufacturers of propanolol delayed two years in submitting data requested by the FDA to demonstrate the safety and efficacy of this drug in hypertension. Suppose the manufacturers never submitted the data? Would that indicate that the drug is not indicated for this illness? Numerous examples can be cited—even in my own limited specialty, neurology (e.g., amitriptyline in prophylaxis of migraine, propanolol in essential tremor). These indications will never appear on the drug inserts if the drug companies don't apply. Does this mean that we should not use these effective and relatively safe therapies and resort to more dangerous drugs approved for these indications? Of course not! Until the FDA and the scientific and medical communities are able to institute additions on their own to the indication section, the package insert will remain a legal and economic document, rather than a valid scientific statement.

Thank you.

SEYMOUR JOTKOWITZ, M.D.
Hackensack, N. J.

On Pauling's Rejection

It was a shocking revelation to learn that a paper by Linus Pauling, twice winner of the Nobel Prize and the most eminent mind in the field of chemistry, was rejected by the editor of JAMA (MT, Mar. 24). And not only that: It appears that prior to being rejected there was a "review" of the manuscript by "a JAMA referee", who dared to suggest some revisions should be made by Dr. Pauling. . . . Does the AMA have any referee who could do something more than shine the shoes of Dr. Pauling?

A. GUTIERREZ DE LUQUE, M.D.
Whitesboro, N.Y.

IN CONSULTATION

What's New and Important In Allergy and Clinical Immunology?

The Consultant

EARL BENEDICT BROWN, M.D.
Assistant Professor of Medicine
Columbia University College of Physicians and Surgeons
New York

THE ESTABLISHMENT of the Board of Allergy and Clinical Immunology was a major advance. This assures the public that a clinical allergist has more than a working knowledge of basic immunology. This Board has set up specific criteria to assure that the future specialist in allergy is a clinical immunologist. The required training will assure much quicker clinical application of immunological facts discovered in the laboratory. Just to cite one example, for many years the standardization of allergen extracts for use in immunotherapy has been chaotic. Some advocate weight by volume. Others vociferously adhere to protein nitrogen units, noon units, total nitrogen and other means. However, as the result of the discovery of immunoglobulin E, we now know the specific protein involved in causing immediate hypersensitivity reactions. Since the purpose of immunotherapy is to neutralize the effect of the IgE antibody, it makes sense to try to standardize the allergen extracts by measuring the amount of antigen necessary to bind the IgE antibody. This is now being done for ragweed antigen, and it is hoped that the same will gradually be done for all other extracts used in immunotherapy.

New forms of testing for atopy, such as the radial allergosorbent test (RAST), are also coming into use. While this particular test is not any more specific than the intradermal testing now used, it replaces the need for passive transfer testing in patients in whom intradermal testing cannot be utilized.

Moreover, immunology is beginning to show evidence of becoming involved in increasing numbers of disease syndromes, and it is perfectly possible to visualize a future in which all of us practicing medicine will be clinical immunologists.

What role does IgE play in the pathogenesis of allergic manifestations?

The reagenic activity in an individual is due principally to immunoglobulins of the IgE class. When IgE antibody combines with the antigen, the resulting complex disrupts the mast cell membranes releasing histamine, SRA and heparin. These chemicals act on the shock organ (e.g., in allergic rhinitis, the mucous membranes lining the nose or sinuses; in bronchial asthma, the bronchial mucous membranes) causing manifestations of the type I allergic disease. Any level of IgE above 250 nanograms per cc is considered elevated. However, elevated levels can occur in numerous other disease syndromes and are not associated only with the allergy. The level of IgE of itself cannot be used to make a definitive diagnosis of the type of allergic reaction occurring. Immediate type allergy could probably be ruled out if the level were normal or below.

What is the reliability of using skin tests for food, drug or animal allergies?

Skin testing is worthless unless it is correlated with a good history and physical examination. It is totally unreliable when testing for food allergy. But it has some reliability when testing for certain drugs, such as penicillin. However, the newer forms of drug testing which utilize the lymphocyte transformation technique are much more reliable. At this time, lymphocyte transformation is a highly sophisticated research technique, not generally available. For the present, diagnosis of a drug allergy depends on an accurate history.

Intradermal testing is about 95% reliable when testing for animal dander sensitivity. If a patient has allergic symptoms and is closely exposed to a furred or feathered animal, but the skin test to the 1000 protein nitrogen unit strength is less than 2+ (reading on a 1 to 4+ scale), I would tend to rule out the animal as the cause of the symptoms. I have never seen a patient with an allergy to an animal that had a negative intradermal test, although the opposite could be true.

In what type of allergies is hyposensitization helpful, and in what types is it not helpful?

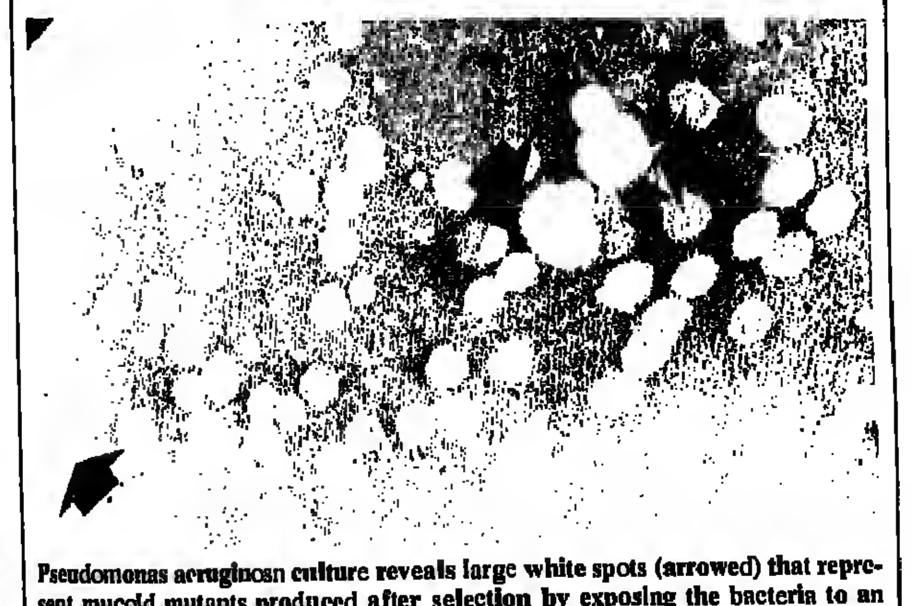
Immunotherapy is helpful when the allergic reaction such as rhinitis or asthma is due to extrinsic causes: pollens, mold spores or house dust, etc. It is not helpful in those patients in whom the symptoms are due to infection or emotional factors.

What are your feelings about the use of cromolyn sodium in the treatment of asthma? When would it be indicated and when would it be of no help? Are there any side effects which would contraindicate its use?

Cromolyn sodium is a useful drug in the prophylactic treatment of asthma. It prevents the antigen-antibody complex from disrupting the mast cell. Cromolyn's use is indicated primarily in the patient whose asthma is due to extrinsic causes and who has been on high doses of corticosteroids. Because of the expense involved and the inconvenience in its use, I do not feel it should be used where the common bronchodilators, in minimal amounts, or where very small doses of steroids (5 mg of prednisone or its equivalent) are effective in the control of the symptoms in adults. It is particularly useful in children in whom asthma control cannot be achieved without the use of corticosteroids. Evaluation should be made at the end of a one-month trial using the medication four times a day.

There are no present known side effects in the use of cromolyn.

Mutant Pseudomonas



Pseudomonas aeruginosa culture reveals large white spots (arrowed) that represent mucoid mutants produced after selection by exposing the bacteria to an antibiotic. Scottish researcher Dr. John Govan conducted studies at Australia's Monash University that suggest certain antibiotics used in treating respiratory infections in children with cystic fibrosis may encourage the evolution of mutants like those illustrated. A disturbing aspect of such mutagenesis is that some Pseudomonas plasmids—nonchromosomal DNA—have the ability to transfer antibiotic resistance to other bacteria.

Next In Consultation

DR. WILLIAM D. DEWYS, Associate Professor of Medicine, Department of Medicine, Oncology Section, Northwestern University Medical School, Chicago, Ill. . . . will discuss the second leading cause of cancer deaths in males—prostatic cancer, recent developments in improved detection and care of such patients, evaluation and recommended treatments of choice, and the problems of treatment in advanced prostatic cancer.

Hypertension/Obesity Relationship Demonstrated in Adolescents

Medical Tribune Report

NEW ORLEANS—The relationship between obesity and hypertension in adolescents has been demonstrated in a Virginia study showing that well over half of a group of hypertensive high school students were in the greater than 97th percentile in weight, whereas less than one-fourth of the total population of students surveyed were in this category.

Forty-eight per cent of the hypertensive black males and 68% of the white males were overweight, but no significant racial differences were found, Dr. Carolyn M. McCue, director of pediatric cardiology at the Medical College of Virginia, told the Second Annual Conference on High Blood Pressure here.

Her report, based on a screening examination of 2323 ninth and tenth grade students in six Richmond high schools, included the following data:

- 1785 adolescents were in Group A, having pressures of 135/88 or less.
- 28 students were in Group B, those with pressures in the 90th percentile, ranging from 141/91 to 160/100.
- 28 students were in Group C, those with pressures in the 95th percentile, at 161/101 or more.
- 124 students were in Group L, those with labile pressures which were elevated on first reading but declined subsequently.

Dr. McCue and other pediatric cardiologists on the team saw most of the students in groups B, C and L. Those in Group C were referred for extensive tests, and their families were urged in written communications to arrange for careful follow-up.

"Clearly studies in children and adults need to be expanded," Dr. McCue said. "We may find the incidence of blood pressure over 140/90 in the adolescent is only 1 or 2%, but more useful is the identification of students with levels over the 90th and 95th percentiles because these are the subjects that need careful follow-up. Revised standards according to age and weight groups should direct us to the children to watch.

"There are many adolescents with labile blood pressure, perhaps 5%, whose pulse rate and blood pressure exceeds normal levels on many occasions, although it may revert to normal quickly. Are these students at risk?"

"Meanwhile, doctors need to take the blood pressure of children beginning with infancy. Patients including adolescents need to be made aware of their blood pressure levels without fear, and all above the 90th percentile should be cautioned to have it followed regularly."

"Let me tell you about the medicine I'm going to prescribe."

TALKING OVER VALIUM®(diazepam) THERAPY WITH YOUR ANXIOUS PATIENT.

A patient often benefits by a greater understanding of his treatment program. You may find it helpful to make your patient aware that the purpose of therapy with Valium is to help reduce discomforting and disabling symptoms of excessive psychic tension and anxiety. It is beneficial for him to understand that much of his tension and anxiety can be relieved by your reassurance and counseling, and that these measures can do more than anything else to help him cope with his basic problems. The patient is reassured in knowing he can expect his medication to help him avoid feeling overwhelmed by his symptoms. And it's also good for him to realize that he will be taking Valium only as long as he needs it.

Your expressed confidence in the medication prescribed, and the positive atmosphere in which therapy is given and accepted, work to the patient's advantage.

"It's important that you follow my directions closely."

Selection of a dosage regimen is an important consideration when Valium (diazepam) is prescribed, and dosage should be individualized to achieve maximum beneficial effect. If the patient understands clearly when and how much to take, and if he knows why it's to his benefit to follow the regimen closely, the chances are better that he will take the medication precisely as directed. That should help avoid missed doses and discourage taking too much or too little medication—all of which can have an undesirable effect on the management of the patient's condition.

"I'll see you again the week after next and we'll see how you're making out."

Your patient is often likely to feel reassured when you talk about seeing him again to check his progress. A planned visit evidences your continued interest and affords the patient an opportunity to report improvement he has made and to relate whatever continuing or additional difficulties he may be experiencing. It's also a chance for him to describe his response to therapy with Valium.

During follow-up visits, as your patient talks about his medication and about its effects on his symptoms, he will provide the kind of information that will be of great help in evaluating total therapy, adjusting the dosage of Valium, or discontinuing the medication entirely if that seems indicated.

Valium® (diazepam)®

2-mg, 5-mg, 10-mg scored tablets

for individualized treatment of psychic tension

ROCHE

Please see the following page for a summary of product information.

Problems of Noise and Sound—Part III of IV

Off the Flat Earth or in Perpetual Orbit

THE WORLD is flat.

I know.

I have published papers that "float out to the edge of the world and then fall off, never to be heard from again." So I wrote some time ago.

The recent recrudescence of interest in sound as n stress phenomenon fascinates me. I have more than a passing familiarity with the literature, having engaged in research in this field. As you will soon appreciate, I've come to the conclusion that most studies are consigned for burial in that great corpus, the medical literature. The unhappy consequences are not just that research efforts are needlessly replicated, but that leads of critical clinical significance are not followed up and potential benefits to patients are lost by default or delayed for decades.

Enshrined or Entombed?

In just one issue of MEDICAL TRIBUNE, two stories made that point. One reported on genetic and metabolic elements in schizophrenia, a subject on which our investigations started over 30 years ago and the findings of which were enshrined (or should I say entombed?) in several dozen papers. The other was on stress phenomena. In this instance sound, an area which has engaged our interest and activity for nearly 20 years.

In respect to the metabolic basis of mental disease, I had been told that our investigations, which pointed to a biochemical, neuroendocrine substrate with congenital as well as genetic factors, were "premature." They came at a time when psychodynamic psychiatry held sway and, therefore, the findings and facts were inconsistent with the fads and fancies of the day. They "just couldn't be." There is no denying the role of trends in science but that still does not explain either the discontinuity or, with the reawakening of interest, the non-referencing to earlier work in new reports.

Wrong Time, Wrong Place

For years past, I felt like a dear friend, Alice in Wonderland, as our group presented physiologic reports at psychiatric meetings only to be greeted with the observation, "What are they doing *here*?" And then we presented physiologic findings in psychiatric states at physiologic forums, including international congresses, only to be greeted with the observation, "What are they doing *here*?" As we sought to convey our findings in publications, those experiences were capped by the observation, "Oh, well, you publish in rather obscure journals."

The next time around, in our work on the quantitation of stress, we thought we would correct past "errors." We were studying sound as one of the unrecognized variables in biologic experimentation and as one of the stress factors we were seeking to quantify. We were excited and sometimes stunned by the changes we observed in the endocrine system and behavior. Our animal experiments revealed, among other changes, marked ovarian alterations with reduction in ovulation (confirmed by B. Zondek and I. Tsmuri in 1960*). We observed changes in adrenal function, body weights, etc. This time we published in such "non-obscure" journals as *Acta Endocrinologica* (Sweden); *Science*, and such a variety of periodicals as *Aerospace Medicine*, *American Zoologist*, *Experimental Medicine and Surgery* (USA); in *Physiology and Behavior*, *Life Sciences* (Britain); *Experientia* (Switzerland) and *Editions du Centre National de la Recherche Scientifique* (France). Our bibliographies carried references to earlier research investigations and the work of many other investigators.

Non-communication Today

Picture my astonishment when MEDICAL TRIBUNE recently reported on its front page an investigation of monkeys with three cohorts, one monkey in each, including the observation of the need for corroborative experiments before one could extrapolate to man. That really did make my head spin. Consider the extensive work on the effects of sound in man and the classic observations of such outstanding men as Sam Rusen and his co-workers.

Just think of the studies that these men alone carried forward, *in vivo*, on the Mabans in the Southeast Sudan, on Dortmunders and Dusseldorfers in Germany; on Yugoslavs in Dalmatia and Finns in Finland, and in two areas which hold so much archaeologic interest for me, Cairo and the island paradise of Crete. Perhaps you can understand why my concern has grown with the years as to the communication or non-communication of medical ideas and discoveries, their integration or non-integration into the body of science and their effects or non-effects on patients as well as political and social patterns.

Heaven knows, there is enough evidence of the frequency and speed with which half-cocked research finds its way to the public in the distorted versions of the mass means of communications. That is a separate problem in itself. The question arises as to what is wrong with scientific communications, not just medical and scientific congresses, national and international meetings, symposia and seminars, but in our media of record, professional periodicals which are so carefully codified in the *Index Medicus* and now enlisted in our computer files.

Frankly, I am at my wit's end. Perhaps my wits are limited, but I would appreciate any suggestions as to how to correct a situation in which scientific communication threatens to be drowned in a sea of paper, findings with critical implications lost, and research replicated without reference to a background vast in extent and great in depth. This experience is not restricted to basic research or theoretical investigations. The findings on schizophrenia, on sound and noise, have major implications clinically and socially. Some call for professional and public recognition, others even legislative and regulatory action. Their implications are as fascinating as they are wide ranging. What is true for schizophrenia and sound is true for many other fields.

At this point I should perhaps update myself, bring myself into the space age and change my metaphor. Who knows *how many papers are rocketed into space, emit a beep or two, and then go into perpetual orbit beyond sight and without sound?*

What is to be done?

*Am. J. Obstet Gynecol. 80:104, 1960

EPIGRAMS - Clinical and Otherwise

We all labor against our own cure, for death is the cure of all diseases.

Sir Thomas Browne (1605-82)
Religio Medici

Medicine on Stamps

Marie Curie

The first woman elected to the French Academy of Medicine, Marie Curie (1867-1934) was born in Warsaw, studied physics in Paris, and with her husband, Pierre, discovered radium and polonium in 1898. Pierre and Marie Curie, together with Becquerel, were the Nobel Prize recipients in physics in 1903 for this important discovery. After her husband's death, Mme. Curie carried on the work alone. Her chemical investigations of radium earned her another Nobel Prize in 1911. Women's Medical College of Philadelphia and the Universities of Cracow and Geneva awarded her honorary degree of Doctor of Medicine. Radium was the first really useful "medicine" in the treatment of cancer, particularly cancer of the uterus.

Text: Dr. Joseph Klar
Stamp: Mlukus Publications, Inc., New York

Logic Behind Court Decision In Quinlan Life-Support Case

Continued from page 3

the criteria of the Harvard Ad Hoc Committee was testified to by Dr. Morse and other physicians.

Reviewing her 24-hour care, her weight loss of 40 pounds, her grotesque fetal-like posture, her tubal feeding, the deformity of her joints, the court observed: "As nearly as can be determined . . . she can *never* be restored to cognitive or sapient life . . . and removal from the respirator would cause her death soon . . . "

Describing futile efforts to wean her from the respirator, the court noted that while physicians believe she cannot survive without the respirator, "It seemed to be the consensus not only of the treating physicians but also of the qualified experts who testified, that removal from the respirator would not conform to medical practices, standards and traditions."

The Court raised the question of how far doctors would go to sustain Karen's existence. It emphasized that physicians make a critical distinction in deciding when to apply life-sustaining measures, citing the testimony of another neurologist, Dr. Sidney Diamond. He distinguished "between respirator support in a major surgical case or transfusion in a terminal case not involving cerebral death."

The court quoted Dr. Diamond's testimony: "The subject has lost human qualities. It would be incredible, and I think unlikely, that any physician would respond to a sudden hemorrhage, massive hemorrhage or a loss of all her defensive blood cells by giving her large quantities of blood. I think that . . . major surgical procedures would be out of the question even if they were known to be essential for continued physical existence."

The court also cited Dr. Julius Korein's testimony on "the medical practice concept of 'judicious neglect' under which the physician will say: 'Don't treat this patient anymore. It does not serve either the patient, the family or society in any meaningful way.'" The Court also noted his descriptions of the unwritten medical practice "implied in the foreboding initials DNR (Do Not Resuscitate) as applied to the extraordinary terminal case of a cancer patient."

Noting the proliferation of malpractice suits and confronting the fact that medical practice standards created in another era forbade the physicians' withdrawal of extraordinary life-sustaining apparatus in a hopeless case, the court insisted: "There must be a way to free physicians in the pursuit of their healing vocation from possible contamination by self-interest or self-protection concerns which would inhibit their independent medical judgments for the well-being of their dying patients."

(Continued Next Issue)

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An open letter to the doctors of America

Subject: **The all-important physician-patient relationship**

Dear Doctor:

We must and will do something about it.

The science and art of medicine has reached its most advanced state but the all-important physician-patient relationship is plunging to an all-time low.

We must do something about it.

The establishment of "cost-effective" control rather than "therapeutic-effective" practice is part of the drive towards the government's dominance, if not takeover, of medicine. Physicians personally, and the medical profession generally; medicines specifically, and diagnostic and other procedures generally, have become a target for governmental attacks as a result of the pressures generated through sensation-seeking consumerism and political expediency.

Patient regimens are too often disrupted, medical advice disregarded and medications neglected. Early diagnosis of essential conditions is being placed in jeopardy and early treatment delayed.

We must do something about it.

Medical Tribune has addressed these issues editorially. Medical Tribune has encouraged the mobilization of official bodies of medicine. It has reported extensively on constructive efforts by *ad hoc* committees of physicians. We have discussed these problems at great length with responsible consumer leaders, leaders in all fields of medicine, and with a whole gamut of government officials.

More is needed.

Medical Tribune has developed and is introducing an innovation in patient education to help rebuild and sustain the all-important physician-patient relationship. Medical Tribune has prepared a series of supplements for use in physicians' waiting rooms, clinics, and hospitals, entitled THE GOOD DRUGS DO. Each supplement is prepared by an outstanding leader in one of the fields of medicine. Each supplement is written so that the patient can understand it. Each seeks to advance the goal of an informed patient, a cooperative patient, and a patient confident in his physician's practices, medicines and recommendations. The waiting room patient supplement, THE GOOD DRUGS DO, will be coming to you as a section of Medical Tribune.

THE GOOD DRUGS DO patient supplement in Medical Tribune seeks to do something positive about the physician-patient relationship.

THE GOOD DRUGS DO supplements prepared thus far consist of a general introduction by Dr. Louis Lasagna, covering the broad advance made by therapeutic medicine in the Golden Age of Therapeutics. THE GOOD DRUGS DO individual supplements then go on to take up Depression, Hypertension, Nutrition and Vitamins, Alcoholism, Diabetes, Arthritis, Psychoses, Antibiotics. Each subject supplement is prepared by an outstanding authority in the field and addressed to patients.

Please remove THE GOOD DRUGS DO supplements from coming issues of Medical Tribune and put them in your waiting room.

You can help us help your patients by making this essential material available to them and by advising us as to how we may make improvements in your and your patients' interests.

We can do something about the all-important physician-patient relationship.

Sincerely,

International Publisher

Coming in the next issue:

Questions on rheumatoid arthritis answered

Tribune Economic Analysis

Market Volume: Investors' Signal To Stop or Go

BY ELIOT JANEWAY
Consulting Economist

"Stop-go" is a familiar economic concept. Recently, the New York stock market has been staging its own version of "stop-go."

Clinically speaking, pulse beats of "stop-go" are considered erratic. Marketwise, however, they have become predictable. They follow a simple rule: high volume fuels rising prices; subsequent lows in volume trigger price jumps. It seems risky, but it is rhythmic.

The market's day-by-day performance of the week of March 22 demonstrates the principle. On Monday, volume was down to 19,410,000 shares. Prices stalled.

Tuesday produced three shares of upside volume for each share of downside volume; and it left the market poised for an explosive breakout.

The fireworks started Wednesday. The 32 million shares traded started a price jump.

On Thursday, volume slowed down to 22 million shares, and the signal for prices reversed from "go" to "stop."

Friday, the market closed out the week with the indicators turned back to where they started from on Monday, to "stop" from "go." This past March was not just another month to the institutional portfolio managers whose buying makes the difference for volume and, therefore, for prices. It marked the end of the first quarter in some time which gave them a chance to look good. They were not about to spoil their performance by knocking prices down just a few days before reporting time. So the market slowed down to a crawl. . . .

Ask Janeway

I have been disappointed with the returns on insurance company stock. I am 45 years old, have a $75,000 annual income, and have no debts, except for a sizable mortgage. I am tired of being told to buy "blue chips." They are going nowhere. I want to double my money in five years. I'd like to invest in electronic instrumentation. Am I wrong?

New Orleans M.D.

You're mixing horses and apples. First, no investors in insurance stocks who know what they are doing expect any returns from them in the normal sense of the word, i.e., dividend income. All insurance stocks pay low returns. Second, the record 1976 market move started when the "blue chips" went to town. Moreover, a number of the "bluest chips" are electronic instrumentation companies.

Send your questions on finances, investments, taxes to Janeway, MEDICAL TRIBUNE, 880 Third Avenue, New York, N.Y. 10022.

'Confusion' Clouds Genetic Counseling Of Diabetic Patients

Continued from page 1

Center and sponsored by the National Foundation-March of Dimes.

Genetic heterogeneity, he pointed out, implies that different genetic and/or environmental factors may result in diabetes—and thus makes it evident that no general formula about recurrence risks will fit all patients and families.

Physicians long ago recognized the clinical variability between juvenile onset and maturity onset forms of diabetes, Dr. Zonana said. Additionally, studies have shown ethnic variability in prevalence and clinical features, and have suggested a role of environmental factors in producing these differences.

Citing more recent evidence for heterogeneity, he listed the following findings:

- A significant association of two histocompatibility antigens—HLA-8 and W15—with juvenile onset but not maturity onset diabetes has been established.
- Studies of identical twins have demonstrated that about 50% of pairs are concordant for diabetes if the index twin developed the disease under the age of 40 (chiefly representing insulin-requiring juvenile onset diabetics). On the other hand, 100% of identical pairs have been concordant if the index twin was over 50 at onset of diabetes.
- A distinct type of diabetes called "maturity onset diabetes of young people" (MODY) is now recognized. These patients show the maturity onset phenotype of few symptoms, no ketonuria, control without insulin, and no progression in severity—yet there is an early age of onset.

Stressing the different pattern of inheritance seen in this last group, Dr. Zonana said that 85% of MODY patients observed in one study had a diabetic parent, half of the sibs who were tested also proved diabetic, and 46% of the families displayed three-generation direct vertical transmission of the trait. Autosomal dominant inheritance is thus suggested.

By contrast, he continued, a study of juvenile onset diabetics has shown that only 11% of their parents were themselves diabetic, eight of 74 sibs were affected, and three-generation transmission was seen in only 6% of cases.

"It should be apparent with the recognition of heterogenicity in diabetes mellitus that no single set of recurrence risks is applicable to all diabetics," Dr. Zonana cautioned.

What about the children of two maturity onset diabetics? According to Dr. Zonana, follow-up of such offspring has shown a relatively low prevalence of diabetes—3% to 12%. More offspring have shown carbohydrate abnormality but 80% of those with latent diabetes who were observed for periods up to 22 years did not develop symptomatic diabetes or experience a worsening of glucose tolerance.

The relationship of diabetes to congenital malformations has also been an area of disagreement and confusion, Dr. Zonana said, but the findings of the Collaborative Perinatal Project have now provided valid data.

Offspring of women with overt diabetes showed a two-fold increase in malformations, both major and minor, he reported. The increase in malformation rate was significantly greater in Caucasian compared to black diabetic women, and the incidence was also significantly higher among children of mothers who had been diabetic for more than five years than among those whose mothers had been affected for a shorter time.

No increase in malformation rate was observed if the mother had gestational diabetes or if the father alone had diabetes.

Dr. Zonana pointed out, however, that the Project findings do not answer questions about heterogeneity among diabetic mothers. For example, did the Caucasian women with overt disease lasting more than five years represent primarily juvenile onset diabetics? And what type of diabetes did the black mothers have?

Summing up guidelines for genetic counseling, Dr. Zonana stressed that the first essential is an accurate diagnosis and determination of the phenotype present in the proband and other affected family members.

He also urged that the seriousness of the given type of diabetes for which offspring is at risk should be considered in counseling, since the burden of juvenile onset diabetes would be far greater than that posed by the MODY type.

A third concern, in his view, is the over-all well-being of the diabetic patient and potential offspring—"the total medical, social, and psychological situation."

And finally, Dr. Zonana cautioned clinicians to recognize the inability of medicine to specify at the present time exact recurrence risks to most diabetics or their families.

Clinical Trials

By Oldden

IMMATERIA MEDICA

The Stress of Selye

A revised edition of Dr. Hans Selye's classic, *The Stress of Life* (McGraw-Hill), sums up in general terms what medicine has learned about stress since Selye outlined the General Alarm Syndrome (GAS) in a paper in *Nature* in 1936.

Selye is, of course, an outstanding medical scientist but his big struggle (stress) has been with words—because there were no medical terms for what he was trying to describe. As he learned more about stress and the body's reaction to it, he altered GAS so that it now means "General Adaptation Syndrome."

When Selye lectured in Paris in 1946, he found himself confronting some of the leading literary men in the College of France—and the anglicized word *stress* had no equivalent in French. The French literati took it most seriously; after eliminating *dommage, aggression, tension,* and *detresse,* they decided the gender would have to be masculine and that the term should *le stress.*

The same thing happened in Germany, Italy, Spain and Portugal—the word becoming, *der Stress, lo stress, el stress,* and *o stress.* Even if his scientific work has little value, says Selye, "Mine will forever be the glory of having enriched all these languages by at least one word."

What His Book Doesn't Tell

What his book doesn't tell is how he gets along with his own stresses. We can't pretend to know, but the stresses have been considerable and plain old vanilla observation shows Selye to have an adaptative sense of humor. His original formulation of "stress" upset a lot of people who were stuck in the germ rut. That stress could be emotional, could even be joy, infection, isolation or running wasn't an easy concept for many physicians, even in the 1950s. Many denied it existed. One British doctor was so upset by its indefinability that he wrote: "Stress, in addition to being itself and the result of itself, is also the cause of itself." Dr. Selye at the time laughed and said, "Stress can't be defined in precise medical terms any better than the word *life.* Yet who would deny life exists?"

But the secret of Selye's management of stress is revealed by his dedication in his massive encyclopedia of endocrinology to his wife, the movie industry and magazine cartoonists "without whose refreshing influence the boredom of this venture could not have been endured."

He brings medical students to attention in lecturing on the general adaptation syndrome—writing "GAS" on the blackboard solemnly. Then turning to the white-coated students, he says, deadpan, "Just gas."

No wonder he's still going strong—and past 70.